RESPONSE TO OFFICE ACTION

A. Status of the Claims

The Action acknowledges Applicants' traverse of the restriction between Group I and Group II and acknowledges the persuasiveness of the traverse. Thus Groups I and II are considered in the Action. The Action makes the previously made species election requirement final. Applicants respectfully request consideration of all species in the case upon the allowability of a generic or linking claim. Claim 50 is amended. Support for this amendment is found in the specification, for instance at page 50, line 13. Claims 41, 43-45, 47-60, 62 and 63 are currently pending in the case and under consideration.

B. Objection to the Specification

(1) The Action objects to the specification as not including a brief description for each of figures 1A, 1B, 1C, and 1D. In response Applicants note that the specification has been amended as noted. The objection is therefore believed moot and withdrawal thereof is thus respectfully requested.

(2) The Action states that the filing date for U.S. Application No. 09/001,157 should be corrected on page 2, line 2 of the specification. In response Applicants note that the specification has been amended accordingly. The objection is therefore believed moot and withdrawal thereof is thus respectfully requested.

C. Amendments to the Specification

In addition to the amendments to the specification mentioned above, Applicants also amended the specification at pages 38 and 51-52 to correct typographical errors.

D. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 41, 43-45, 47-60, 62 and 63 are rejected under 35 U.S. C. § 112, second paragraph as indefinite. In particular, it is stated that the method of claim 1 is not clearly defined in that one would interpret the claim to read on administration of both a nucleic acid and an antigen to a subject. It also stated that the claim would read on administration of a nucleic acid to elicit an immune response without expression of the antigen and that DNA vaccination and antigen vaccination are different methods involving different molecular interactions.

In response Applicants note that claim 41 recites a method for vaccinating a subject, comprising obtaining either a nucleic acid encoding an antigen, or an antigen that is encoded by said nucleic acid. Applicants also note that step (a) describes a method for determining whether a nucleic acid elicits an immune response (*i.e.* by ELI, Expression Library Immunization, involving expression of a nucleic acid coding sequence; the nucleic acid is not the antigen *per se*), or an antigen elicits an immune response (*i.e* upon its expression from a library member). Thus, either a nucleic acid encoding an antigen, or an antigen, may be administered in step (b), following determination of elicitation of an immune response due to administration of member(s) of a nucleic acid library in step (a).

One of skill in the art would understand that "DNA vaccination" is not performed in order to directly immunize a subject against a nucleic acid molecule. Rather, it is performed to provoke a response against a peptide or protein encoded and expressed, at some level, by the nucleic acid molecule (*e.g.* specification at page 27, lines 1-4). Thus vaccination with DNA would not be understood to involve an interaction with a "DNA antigen." DNA vaccination and antigen vaccination, noted by the Action at page 4, middle paragraph, would both be understood to involve the same molecular interaction, a protein-protein interaction- a humoral and/or cellular

immune response conferred by a peptide or protein antigen encoded by the administered nucleic acid.

Applicants also note that, regardless of whether a nucleic acid encoding an antigen, or an antigen, is administered to a subject in step (b), step (a) recites a method for first determining whether an immune response has been elicited, in which a nucleic acid or antigen is administered using the same reagent (nucleic acid library member(s))and step (introducing a plurality of members of the library into an animal). As noted in the Action, an identified protein (or peptide) may be administered directly to a subject in step (b) without a nucleic acid.

The Action's comment regarding techniques for identification of nucleic acid as differing from techniques for identifying a protein antigen is unclear. However, by being identified through use of a nucleic acid library in step (a), the claimed method for identifying a protein antigen comprises the same steps as the method for identifying the nucleic acid which encodes that protein (or peptide) antigen. Finally, the administration procedure for vaccination with DNA or with an antigen in step (b) may or may not differ in routine details known to one of skill in the art of formulation and administration of vaccines. Applicants thus submit that claim 41 and those depending from it are distinctly claimed, and respectfully request that the rejection be withdrawn.

E. Rejection Under 35 U.S.C. § 112, First Paragraph – Written Description

The Action rejects claims 41, 43-45, 47-60, 62 and 63 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. In particular it is asserted that, while the specification provides examples of an expression library generated from bacteria and administering this to an animal/subject, the specification does not provide adequate written

description for the full scope of the invention. In particular, it is stated that only description for one particular bacterial gene library and one particular species of animal are provided and thus the full scope of the claims is not described. For example, it is asserted that procedures for isolation and fragmentation of DNA from other species of pathogens may differ in method and administration may differ in different animals.

In response, Applicants note initially that the characterization of the method found in the Action at point 10, page 5, 2nd paragraph (lines 9-13), appears inaccurate. In particular, the claimed method recites a method for identifying a nucleic acid from a library that codes for an antigen that elicits an immune response, and/or the encoded antigen. That is, the nucleic acid that elicits an immune response does so by being expressed in a subject to yield a protein or peptide antigen. Further, the method comprises administration of either the identified nucleic acid or the antigen encoded by it, to a subject.

The Action asserts that only one bacterial gene library is described in detail in the specification. Applicants respectfully traverse, in that Example 2 describes creation and use of a *Mycoplasma* library, while Example 3 described creation and use of a *Listeria* library. Thus libraries from two distinct organisms are described, and it is explicitly noted that detailed knowledge of the biological properties of a pathogen (other than its genome size) are not required (specification, page 17, line 25, to page 18, line 30). Perhaps surprisingly, even the unusual codon usage of *Mycoplasma pulmonis* (page 49, line 25) did not interfere with the efficacy of the method. Further, the use of the mouse as a model organism for immune studies is well known in the art, as is the applicability of results from such a mouse model in other animals. MPEP 2163 (II) 3 further states that

> Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession

> of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., *Eli Lilly*. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.

In this instance, a method of vaccination is described and claimed, wherein an antigen or the nucleic acid that encodes an antigen is identified. Methods for creation of gene libraries, isolation and fragmentation of genomic DNA, and formulation and injection of materials into different subjects are also explicitly described (*e.g.* at pp. 19-20), incorporated by reference (*e.g.* pp. 25-29), or well known in the art. A detailed application of the method for immunizing against two distinct organisms is described. Applicants respectfully submit that the disclosure in the specification, in combination with the knowledge of one skilled in the art, adequately supports the claimed genus. MPEP 2163 (II) 3 (a) (ii), *Rasmussen*, 650 F.2d at 1214,211 USPQ at 326-27. Withdrawal of the rejection is respectfully requested.

F. Rejection Under 35 U.S.C. § 112, Second Paragraph

The Action rejects claims 50, and 54-58 as allegedly indefinite. In particular it is asserted that the term "about" is indefinite as not clearly stating the range within which the recited number can vary. In response, Applicants traverse, and note that the term "about" has repeatedly been found sufficiently definite in decisions by the Court of Appeals for the Federal Circuit and the Board of Patent Appeals that are legally binding on the Patent Office. For example, The term "about" used to define the area of the lower end of a mold as between 25 to about 45% of the mold entrance was held to be clear, but flexible. *Ex parte Eastwood*, 163 USPQ 316 (Bd. App. 1968). Similarly, in *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ

303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" is definite. *See also* MPEP 2173.05(b).

Applicants further respectfully submit that one of skill in the art would clearly understand the use of the term "about" in these claims, in light of the specification and the state of knowledge in the art. For instance, in claim 50 regarding isolation of genomic DNA fragments of "about" 400 bp following physical fragmentation or restriction enzyme digestion (specification page 7, line 21 and following), one of skill would clearly understand the meaning of the term, in that an exact fragment size would not be determined for each and every library member insert. Claim 50 has been amended to more clearly claim the Applicants' invention. The amendment does not narrow the scope of the claim, and Applicants do not intend to disclaim any subject matter by the amendment. In claims 54-56, regarding the size of a genetic library, again one of skill would understand that the size of a genetic library is calculated as an approximate number of members, for instance based on a count of phage plaques or bacterial colonies following a dilution series. To describe it otherwise than as an approximation in order of magnitude would imply a false sense of precision and simply not make sense to one of skill in the art. Likewise, the recited DNA or RNA amounts in claims 57-58 reasonably apprise those of ordinary skill in the art of the scope of the claimed invention. *See e.g.,* MPEP 2173.05(b). Withdrawal of the rejection is respectfully requested.

G. Rejection for Non-Statutory Double Patenting

The Action rejects the claims under the judicially created doctrine of obviousness-type double patenting over each of U.S. Patent Application No. 10/023,437, U.S. Patent No. 5,703,057 and U.S. Patent No. 6,410,241. Regarding the '057 patent, Applicants note that a

terminal disclaimer will be submitted upon indication of allowable subject matter. Regarding the '437 application, Applicants note that a terminal disclaimer will be submitted upon indication of allowable subject matter, if needed in view of any issued claims from the '437 application. Regarding the '241 patent, Applicants respectfully traverse as follows:

Cited claims 1-28 of the '241 patent describe methods of screening open reading frames to determine their capability of generating an immune response in an animal. However, claim 1 (b) explicitly states that an introduced expression element is to be introduced into an animal without intervening cloning or bacterial propagation. No genetic library is being utilized for administration into a subject. In contrast, the claims of the present application require the administration of a genetic library into a subject. Thus, applicants submit that the inventions as claimed are distinct, and respectfully request that the rejection be withdrawn.

H. Rejections Under 35 U.S.C. § 102

(1) The Action rejects claims 41-43-45, 47-50, 54-56, 59 and 62 as allegedly anticipated under 35 U.S.C. § 102(b) by Lai *et al.* (*Vaccine.* Vol. 12:291-298; March, 1994). For example, it is asserted that Lai *et al.* teach screening a library of constructs from *Mycoplasma pulmonis*, immunizing animals with selected constructs against *Mycoplasma pulmonis*. It also teaches the construction of a library using sheared DNA and use of *E. coli* for preparing the host library. Further it is stated that the reference teaches injection the bacterial suspension into mice and "would refer to administer (sic} the nucleic acid to a subject." Action at page 10.

In response Applicants traverse, and note that Lai *et al.* screened their genetic library *in vitro* (*see e.g.,* p. 294 col. 1). Constructs (library members) that had been pre-selected based on the *in vitro* immunological screen were then introduced into an animal to study their

immunogenicity. Thus, Lai *et al.* in no way teach the method of claim 1, in which the screen (claim 1, step (a)) is carried out *in vivo*. Applicants respectfully request that the rejection be withdrawn.

(2) The Action rejects claims 41, 45, 47, 48, 59, 60 and 62 under 35 U.S.C. § 102(a) as anticipated by Coney *et al.* (*Vaccine.* Vol. 12:1545-1550, 12/1994). For example it is asserted that Coney *et al.* teach administering DNA to rodents and non-human primates to elicit immune responses against HIV antigens. Specifically, it is asserted that the reference teaches production of several DNA constructs encoding various HIV proteins and that this would meet the limitation of "obtaining a library comprising DNA or RNA sequences from a pathogen" and further teaches administering the construct thus allegedly reading on "introducing a plurality of members of said library into an animal..." thus alleging that the claims are anticipated.

In response, Applicants traverse. The Action asserts that Coney *et al.* describe production of several DNA constructs encoding various HIV proteins (page 1546, right column, 3rd paragraph). The cited description does not describe use of a genetic library. Rather, it describes the use of pre-selected coding regions from only specific gp160 envelope glycoproteins, or *gag* or *pol* genes. These specific coding regions were not selected *in vivo* from a library of DNA or RNA sequences as recited in the current claims. The Action also described administering constructs either separately or together (page 1547, left column, paragraph 2). Again, no genetic library is described or utilized. Rather, specific inserts were cloned and administered. Furthermore, this reference's screening for immunogenicity is not described to occur via a method of *in vivo* screening of a plurality of genetic library members. In view of this, Applicants respectfully submit that the present claims are not anticipated, and withdrawal of the rejection is thus respectfully requested.

I. Rejection Under 35 U.S.C. § 103(a)

The Action rejects claims 41, 43-45, 47-60, 62 and 63 under 35 U.S.C. § 103(a) as obvious over Lai *et al.* (*Vaccine.* Vol. 12:291-298; March, 1994) in view of Felgner *et al.* (U.S. Patent No. 5,589,466). For example it is asserted that Lai *et al.* teaches screening a library of DNA constructs derived from *Mycoplasma pulmonis* and immunizing animals with constructs against this pathogen. It is further stated that although Lai *et al.* do not teach that the DNA sequence of a pathogen is fused to a mammalian fusion gene and that the expression construct contains a promoter or teach a specific amount of DNA or that the DNA is chemically synthesized, Felgner *et al.* teach these limitations. It is further stated that Felgner *et al.* provides motivation to combine the references and thus it would be obvious to combine the references to arrive at the invention.

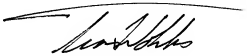
In response, Applicants traverse, and submit that, as noted above, Lai *et al.* do not describe *in vivo* screening of a library of DNA constructs derived from *M. pulmonis*. Felgner *et al.* likewise do not describe such a method. Rather, they describe delivering isolated polynucleotide (*e.g.* abstract, line 1) to exert a therapeutic effect. Each of the examples that describes administration of a polynucleotide does so with respect to a specific coding sequence, such as a CAT gene, or a dystrophin gene. This is in contrast to the presently claimed method, in which the polynucleotide(s) screened in step (a) of claim 1 is not isolated or identified prior to the screening step, but is among a plurality of library members. The cited references do not teach every element of the claims, and thus Applicants respectfully submit that the teachings of Lai, in view of Felgner, do not render the present claims obvious. Withdrawal of the rejection is thus respectfully requested.

CONCLUSION

This is submitted to be a complete response to the referenced Office Action. In conclusion, Applicant submits that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested.

The Examiner is invited to contact the undersigned at (512) 536-5654 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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